

High endothelial venules

Help or hindrance in the quest for antitumor immunity?

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Recently, a number of studies have documented the presence of high endothelial venules in both mouse and human tumors. The significance of these highly specialized blood vessels within neoplastic lesions, and notably their capacity to influence anticancer immune responses and tumor progression, remains to be fully understood.

Using a well-established mouse model of chemical carcinogenesis (methylcholanthrene, MCA),¹ we have recently demonstrated that the specific ablation of Foxp3⁺ regulatory T cells (Tregs) can result in markedly reduced tumor growth rates and even tumor regression (in some animals).² Unexpectedly, the ability of Treg-depleted mice to control disease progression was not associated with the degree of immune activation but with the extent of intratumoral T-cell infiltration. Moreover, we observed an absolute correlation between the levels of tumor-infiltrating T cells and presence within neoplastic lesions of specialized blood vessels, namely high endothelial venules (HEVs). What is therefore the significance of intratumoral HEVs? These vessels, which are normally found in secondary lymphoid organs, allow naïve T cells and central memory cells to enter lymph nodes upon interactions between CD62L and ligands expressed on HEV. HEVs have also been observed at sites of chronic inflammation and in autoimmune lesions (reviewed in ref. 3). It is indeed possible that HEVs contribute to the pathogenesis of these diseases by sustaining the accumulation of T cells at the diseased site, hence contributing to the chronicity of the immune response and promoting tissue damage. Nevertheless, HEVs may be useful in tumors as the sustained ingress of T cells into the neoplastic

lesion may promote effective antitumor immune responses. This hypothesis is supported by our own findings in mice as well as by recent reports indicating that intratumoral HEVs are associated with a good prognosis in breast cancer patients.⁴

What is the significance of our findings, originating from a mouse model of MCA-induced carcinogenesis? First, we observed HEVs within neoplastic lesions only after the depletion of Tregs. Thus, at least in this model, the removal of Tregs is an essential prerequisite to the development of HEVs.² These data point to a potential link between Tregs and the differentiation of blood vessels. Perhaps, Tregs prevent the neogenesis of HEVs in conditions of chronic inflammation by limiting dendritic cell activation and/or the production of pro-inflammatory cytokines such as lymphotoxin $\alpha\beta$ (LT $\alpha\beta$).

Second, we only observed HEVs within the neoplastic lesions of a fraction of Treg-depleted animals. This finding indicates that while the depletion of Treg may be necessary for HEV development, it is certainly not sufficient.² Why HEVs develop in the tumors of some, but not all, Treg-depleted mice remains to be clarified. The mechanism(s) that account for this observation may be linked to the nature of the immune response that develops upon the depletion of Tregs. For instance, the T cells and/or B cells of some, but not all, mice

might produce LT $\alpha\beta$ or other important HEV-inducing factors.⁵ Alternatively, the development of HEV may be dictated by the nature of developing tumor. For instance, the tumor might specifically impinge on the immune response or it might produce factors that favor or inhibit HEV formation. The identification of the mechanisms that underlie the development of intratumoral HEVs may provide valuable clues for harnessing HEV to boost anticancer immune responses in several settings.

Our studies as well as reports describing the prognostic significance of HEVs in melanoma and breast cancer patients ascribe beneficial effects to intratumoral HEVs. A note of caution, however, comes from an elegant report by Shields and colleagues. By means of tumor cell lines engineered to produce varying levels of the chemokine CCL21, the authors of this study demonstrated that the development of lymphoid-like features (including HEVs) within tumors conferred on them the ability to inhibit anticancer immune responses by enabling the entry of Tregs and myeloid derived suppressor cells (MDSCs).⁶ These data are particularly interesting in light of a previous study by Schneider and colleagues, who examined the impact of CCR7 deficiency on the development of adaptive immune responses. Surprisingly, the authors found that antigen-specific T-cell responses were delayed but actually

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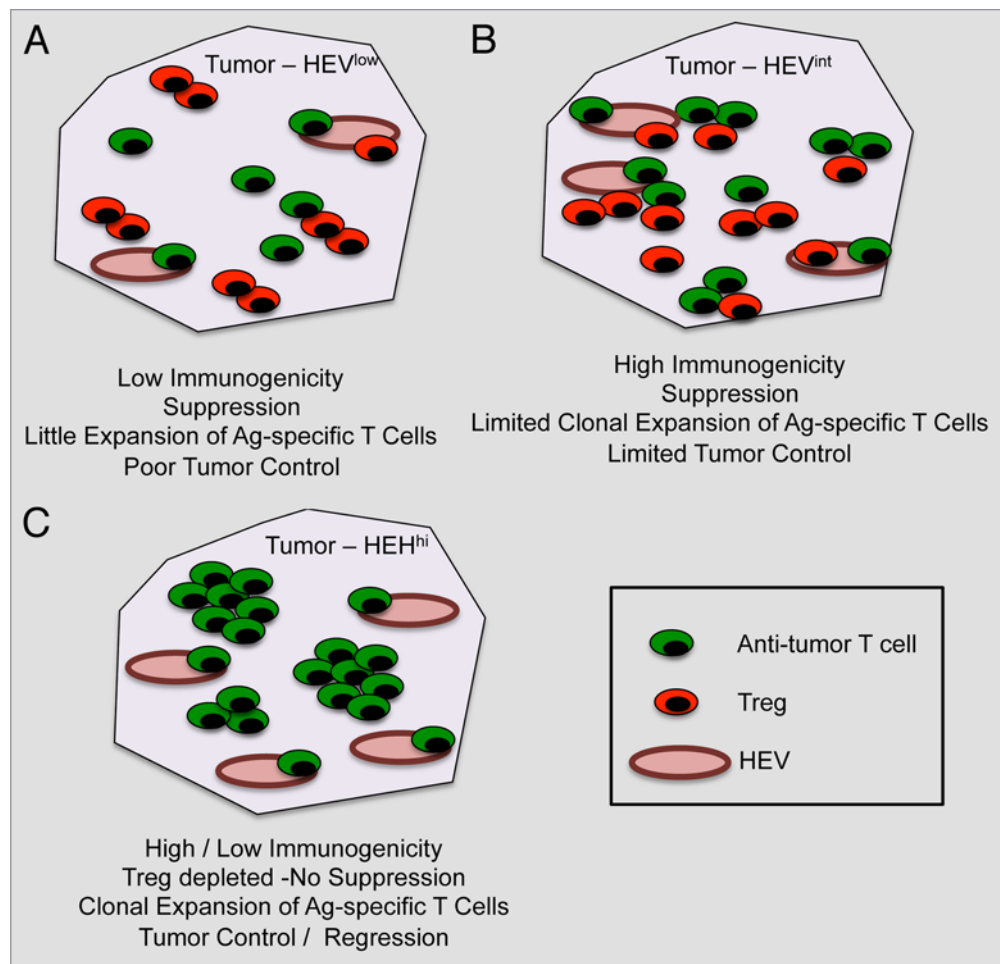


Figure 1. Impact of high endothelial venules on tumor progression. (A) In the case of poorly immunogenic tumors, high endothelial venules (HEVs) are not abundant (HEV^{low}) and the neoplastic lesion is infiltrated by both conventional T cells and Foxp3⁺ regulatory T cells (Tregs). In this setting, antitumor T cells have limited chances to expand and tumor growth remains virtually unaffected. (B) When tumors are highly immunogenic, the number of intratumoral HEVs is slightly increased (HEV^{int}), resulting in a relatively more intense recruitment of conventional T cells and Tregs. In this case, tumor-specific T cells may undergo some expansion, yet the presence of Tregs limits their antineoplastic effects. (C) The depletion of Tregs not only limits immunosuppression but also greatly increases the number of intratumoral HEVs (HEV^{hi}). This results in the elicitation of robust antitumor immune responses that can control disease progression (at least theoretically) irrespective of the immunogenicity of malignant cells.

increased in *Ccr7*^{-/-} mice, as compared with their wild-type littermates.⁷ Moreover, the major impact of CCR7 deficiency reflected an impaired immune regulation stemming from a dramatic decrease in the abundance of Tregs within lymph nodes of *Ccr7*^{-/-} mice. These data point to a tolerogenic role for CCR7 and its ligands, CCL19 and CCL21, and explain why the intratumoral expression of these chemokines might facilitate immunosuppression, as suggested by Shields and colleagues. Thus, the presence of HEVs may not always be indicative of a microenvironment that supports productive antitumor immune responses.

Collectively, the results of these studies suggest that simply inducing HEVs in tumors is not sufficient to activate

antitumor immune responses. These will indeed depend upon the inherent immunogenicity of malignant cells as well as upon the presence of local signals for the priming of antigen-specific T cells. Hypothetically, in the case of a poorly immunogenic tumor, HEVs may promote the recruitment of both conventional T cells and Tregs, which would presumably result in a limited expansion of tumor-specific T cells and no control of tumor progression (Fig. 1A). Conversely, in the case of highly immunogenic tumors, the expansion of tumor-specific T cells may occur in spite of the concomitant ingress of both Tregs and conventional T cells via HEVs, resulting in a moderate control of tumor progression (Fig. 1B). Our study suggests

that Treg depletion lowers the threshold for both immune cell activation and HEV neogenesis, the overall effect of which is the elicitation of robust antitumor T-cell responses, perhaps even when tumors are of low immunogenicity (Fig. 1C). This results in a significant control of tumor progression and, at least in some cases, tumor regression. Should this model be confirmed by independent studies, combining Treg-depleting regimens with strategies for the intratumoral neogenesis of HEVs may turn out to constitute a highly effective form of cancer immunotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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